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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,509	06/25/2001	Fritz Grunert	24741-1523	9439

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EXAMINER	
CHEN, LIPING	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,509	GRUNERT ET AL.	
	Examiner	Art Unit	
	Liping Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Liping Chen of Group Art Unit 1632.

Status of the claims

A restriction was made on 09/18/2002. Applicant's election with traverse of Group IV, claims 1-17 and 18 in part, in Paper No. 5, is acknowledged. For a further consideration, the lack of unity requirement is withdrawn. Therefore, all groups including claims 1-18 are examined in the office action.

Claims 1-18 are pending and are examined in this office action on the merits.

Priority

This application is filed on 06/25/2001,

which is a 371 of PCT/UEP99/08678, filed 11/11/1999.

Foreign application priority claimed to Germany 198 52 800.0, filed 11/16/1998.

Objection

The disclosure is objected to because of the following informalities:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title causes confusion as how a polypeptide recognizes the coding nucleic acid.

The abstract of the disclosure is objected to because it comprises four paragraphs. An abstract should contain only a single paragraph on a separate sheet within the range of 50 to 150 words. Correction is required. See MPEP § 608.01(b).

Claim 3, states "His_6, tag sequence". It is suggested this be written to state "His_6 tag sequence".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: step (a) omits a

polypeptide isolation step, so that the isolated polypeptide can be bound to a solid phase with the aid of the detection signal; step (b) omits an antibody purification step.

Claim 1, as written is indefinite as using the term of "wherein the nucleic acid encoding the polypeptide is known". There is no antecedent basis in the claim for "the nucleic acid". The depending claims 2-17 are rejected to for being dependent on indefinite claim.

Claim 1, as written is indefinite as using the term of "the DNA encoding the polypeptide" in step (a). There is no antecedent basis in the claim for "the DNA". The depending claims 2-17 are rejected to for being dependent on indefinite claim.

Claim 1, as written is indefinite as using the term of "for the purpose of preparing the desired antibodies, is also used in vitro for producing the target protein". It is not clear if this is distinct from step (a) or repeat of step (a). The depending claims 2-17 are rejected to for being dependent on indefinite claims.

Claim 1, as written is indefinite as using the term of "using a vector which possesses at least one sequence encoding a detection signal". It is not clear if this signal is operatelly linked to the nucleic acid encoding the polypeptide. The depending claims 2-17 are rejected to for being dependent on indefinite claims.

Claim 7, as written is indefinite as using the term of "which is introduced directly into an animal in accordance with step (b) is present in a vector". It is not clear if this vector is the same as the vector of claim 1 or a different vector.

Claim 7, as written is indefinite as using the term of "the polypeptide-encoding DNA". There is no antecedent basis in the claim or the claim from which it depends for "the polypeptide-encoding DNA".

Claim 8, as written is indefinite as using the term of "the polypeptide-encoding DNA". There is no antecedent basis in the claim or the claim from which it depends for "the polypeptide-encoding DNA".

Claim 10, as written is indefinite as using the term of "the polypeptide-encoding DNA". There is no antecedent basis in the claim or the claim from which it depends for "the polypeptide-encoding DNA".

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: step (a) omits how to isolate the polypeptide so that the isolated polypeptide can be bound to a solid phase with the aid of the detection signal.

Claim 18, as written is indefinite as using the term of "wherein the nucleic acid encoding the polypeptide is known". There is no antecedent basis in the claim for "the nucleic acid".

Claim 18, as written is indefinite as using the term of "the DNA encoding the polypeptide" in step (a). There is no antecedent basis in the claim for "the DNA".

Claim 18, as written is indefinite as using the term of "for the purpose of preparing the desired antibodies, is also used in vitro for producing the target protein". It is not clear if this is distinct from step (a) or repeat of step (a).

Claim 18, as written is indefinite as using the term of "using a vector which possesses at least one sequence encoding a detection signal". It is not clear if this signal is operatelly linked to the nucleic acid encoding the polypeptide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 18 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Wright, Jr. (U.S. Patent No. 5,639,656, issued 06/17/1997).

Wright, Jr. ('656) provides monoclonal antibodies (MAbs) directed against a highly restricted biological marker benign prostate hyperplasia (BPH), hybridoma cells secreting such MAbs as well as associated polyclonal antibody ('656, col. 3, line 11-14, col. 1, line 23, and claims). Thus, '656 clearly anticipates the claimed invention.

It is noted that product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 9-11 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al. (U.S. Patent 5,736,524, issued 04/07/1998) in view of Letesson et al. (Clin Diag Lab Immunol 4:556-564, 1997) and further in view of Ausubel et al (Short Protocols in Molecular Biology, 3rd Edition, Wiley & Sons Inc. 1995, see pages 16.3-5 and 16.58-62).

Claims 1 and 7 are directed to a process for producing antibodies by (a) expressing a polypeptide which possesses at least one sequence encoding a detection

signal, and binding the expressed polypeptide to a solid phase with the aid of the detection signal, (b) independently of step (a), introducing an expression vector comprising a nucleic acid encoding a polypeptide into an animal, wherein the animal produces antibodies against the expressed polypeptide, and (c) the antibodies produced in step (b) will be detected by binding the polypeptide bound to a solid phase of step (a); claims 2 and 3 are directed to the detection signal of claim 1 is at the C-terminus of the nucleic acid (claim 2) and is His_6 tag sequence (claim 3); claims 5 and 6 are directed to the expression vector of claim 1 comprises a strong promoter (claim 5) such as cytomegalovirus promoter (claim 6); claims 9 is directed the animal of claim 1 is a mouse; claims10-11 are directed to the process of claim 1 further comprises administering a genetic adjuvant (claim 10) such as cytokine (claim 11); claim 14 is directed the solid phase of claim 1 is microtiter plate; and claim 15 is directed to the detection of the antibody produced by the animal of claim 1 using an antibody against the antibody after it binds to the polypeptide bound to a solid phase.

Content et al. ('524) teach the production of antigen 85A-specific antibodies in DNA-vaccinated mice ('524, col. 5, line 33-34 and Fig. 9) by injecting a eukaryotic expression vector containing protein-coding DNA sequences ('524, col. 4, line 66 to col. 5, line 1, and col. 7, line 20-24) using different transcriptional promoter such as cytomegalovirus promoter ('524, col. 6, line 50-51, pertaining to instant claims 5-6) and terminators ('524, col. 6, line 25-28) into the animal. Moreover, Content et al.

teach that the injected DNA can be naked ('524, col. 9, line 28), or can be injected with an adjuvant ('524, col. 9, 36-37) such as cytokines GM-CSF ('524, col. 9, line 22-27, pertaining to instant claims 10-11). Content et al. further teach to provide a heterologous leader peptide sequence for secreted and/or membrane proteins ('524, col. 12, line 11-12). However, Content et al. dose not teach using His_6 tag sequence for binding to solid phase such as microtiter plate for antibody detection.

Letesson et al. teaches an Elisa procedure for detecting antibody by coating microtiter plates (Maxisorp; Nunc A/S, roskilde, denmark) with recombinant protein containing a hexahistidine peptide at the C-terminal (Letesson, page 557, left col. last full parag., pertaining to instant claims 2-3 and 14), and biding of antibody can be visualized by using a secondary antibody against the IgG of the animal used for antibody production (Letesson, page 558, left col. 5th full parag., pertaining to instant claim 15). Letesson et al. cures the deficiency of Content et al. in that it teaches a method of fusing His_6 tag as C-terminal signal sequence for coating polypeptide containing His_6 tag to a Maxisorp microtiter plate for antibody detection. However, Letesson et al. does not teach to express protein using mammalian cells.

Ausubel teaches a method for transforming prokaryotic and eukaryotic host cells with plasmid and viral expression vectors to produce or express the protein of interest (Ausubel, pages 16.3-5 and 16.58-62). Ausubel further teaches that mammalian cells are often used as hosts for expression of genes obtained from

higher eukaryotes because the signals for synthesis, processing, and secretion of these proteins are usually recognized (Ausubel, page 16.58, first parag.)

One of skill in the art of antibody production will be motivated to combine the teachings of Content et al. ('524) with the teaching of Letesson et al. and Ausubel to express gene obtained from higher eukaryotes in a mammalian cell using polyhistidine tag because polyhistidine tag enables a simple method for purification and detection of expressed polypeptide (Letesson, page 556, abstract) and expressing genes obtained from higher eukaryotes in mammalian cell will ensure a better signals for synthesis , processing, and secretion of the protein (Ausubel). The level of skill in the art is very high, such that one of skill in the art would be able to modify the teaching of Letesson et al. to express a polypeptide of interest with His_6 tag signal sequence at C-terminal in mammalian cells such as COS cells taught by Ausubel for detection of antibody produced by Content's method with a reasonable expectation of success. Therefore, at the time the invention was made it would have been prima facie obvious to modify the teaching of Content et al. by detecting antibody produced using a mammalian cell expressed polypeptide containing His_6 tag bound to a microtiter plate as taught by Letesson et al. and Ausubel.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al. (U.S. Patent 5,736,524, issued 04/07/1998) in view of Letesson et al. (Clin Diag Lab Immunol 4:556-564, 1997) and Ausubel (Short Protocols in

Molecular Biology, 3rd Edition, Wiley & Sons Inc. 1995, see pages 16.3-5 and 16.58-62) and further in view of Wands et al. (U.S. Patent 6,025,341, issued 02/15/2000).

Claims 1 is directed to a process for producing antibodies by (a) expressing a polypeptide which possesses at least one sequence encoding a detection signal, and binding the expressed polypeptide to a solid phase with the aid of the detection signal, (b) independently of step (a), introducing an expression vector comprising a nucleic acid encoding a polypeptide into an animal, wherein the animal produces antibodies against the expressed polypeptide, and (c) the antibodies produced in step (b) will be detected by binding the polypeptide bound to a solid phase of step (a); claim 4 is directed to the vector encoding the polypeptide of claim 1 possesses a polyadenylation sequence at the C-terminal end of the detection sequence.

The process of producing antibody is rendered obvious in view of Content et al. ('524), Letesson et al. and Ausubel for the reasons previously discussed. Content et al. ('524) teaches to use different transcription terminator in the expression vector ('524, col. 6, line 25-28). Content does not teach to use polyadenylation sequence at the C-terminal end of the detection sequence.

Wands et al. ('341) teaches a method of immunizing an individual susceptible to hepatitis B virus (HBV) by administering a pharmaceutical composition comprising a recombinant nucleic acid molecule which comprised a nucleotide coding sequence that encodes a fusion protein ('341, col. 5, line 60-66) as well as initiation and termination signals operably linked to regulatory elements including

a promoter and polyadenylation signal ('341, col. 7, lines 14-22). Polyadenylaiton sequence is the most common terminal sequence used in the art. The skilled artisan will know to link it at the end of polypeptide coding sequence, such as at the C-terminal of a detection sequence encoding His_6 for transcription termination. Thus, the claimed invention as a whole is clearly prima facie obvious at the time the invention was made.

Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al. (U.S. Patent 5,736,524, issued 04/07/1998) in view of Letesson et al. (Clin Diag Lab Immunol 4:556-564, 1997) and Ausubel (Short Protocols in Molecular Biology, 3rd Edition, Wiley & Sons Inc. 1995, see pages 16.3-5 and 16.58-62) and further in view of Barry et al. (Vaccine, 15:788-91, 1997).

Claim 1 is directed to a process for producing antibodies by (a) expressing a polypeptide which possesses at least one sequence encoding a detection signal, and binding the expressed polypeptide to a solid phase with the aid of the detection signal, (b) independently of step (a), introducing an expression vector comprising a nucleic acid encoding a polypeptide into an animal, wherein the animal produces antibodies against the expressed polypeptide, and (c) the antibodies produced in step (b) will be detected by binding the polypeptide bound to a solid phase of step (a); claim 8 is directed to the process of claim 1, wherein the polypeptide-encoding DNA is introduced into the animal using a gene gun.

The process of producing antibody is rendered obvious in view of Content et al. ('524), Letesson et al. and Ausubel for the reasons previously discussed. Content et al. ('524) does not teach to use gene gun to introduce the vector comprising the polypeptide to an animal.

However, Barry et al. teach that the first step in genetic immunization is transfection of cells *in situ*. It appeared that only muscle cells could take up naked DNA from solution and be transfected. To transfect other tissues efficiently, a gene gun had to be used (Barry, page 790, left col. first full parag.). Thus, it would be prima facie obvious for a skilled artisan to introduce a nucleic acid encoding a polypeptide using a gene gun for delivery the nucleic acid to any non-muscle tissues with a reasonable expectation of success.

Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al. (U.S. Patent 5,736,524, issued 04/07/1998) in view of Letesson et al. (Clin Diag Lab Immunol 4:556-564, 1997) and Ausubel (Short Protocols in Molecular Biology, 3rd Edition, Wiley & Sons Inc. 1995, see pages 16.3-5 and 16.58-62) and further in view of Kilgannon et al. (U.S. Patent No. 7,773,293, issued 06/30/1998).

Claim 1 is directed to a process for producing antibodies by (a) expressing a polypeptide which possesses at least one sequence encoding a detection signal, and binding the expressed polypeptide to a solid phase with the aid of the detection

signal, (b) independently of step (a), introducing an expression vector comprising a nucleic acid encoding a polypeptide into an animal, wherein the animal produces antibodies against the expressed polypeptide, and (c) the antibodies produced in step (b) will be detected by binding the polypeptide bound to a solid phase of step (a); claim 12 is directed to the process of claim 1 wherein suitable cells from an animal with has been immunized are used for preparing hybridom cells for forming monoclonal antibodies.

The process of producing antibody is rendered obvious in view of Content et al. ('524), Letesson et al. and Ausubel for the reasons previously discussed. Content et al. ('524) does not teach preparing hybridoma cells for monoclonal antibody production.

However, Kilgannon et al. ('293) teach using the spleen ('293, col. 15, line 26) of Balb/c mice immunized by subcutaneous injection with ICAM-4 domain-2/GST fusion protein (('293, col. 15, line 14-25) and NS-1mycloma cells ('293, col. 15, line 40) for monoclonal antibody production ('293, col. 15, line 14 to col. 16, line 62). Kilgannon et al. does not use a nucleic acid encoding a polypeptide for immunization which is taught by Content et al. Since it is well know in the art that purification of nucleic acid is much simpler than purification of protein, and immulization of an animal can be achieved by introducing nucleic acid encoding a polypeptide, therefore it would be prima facie obvious for a skilled artisan to

introduce the nucleic acid encoding the polypeptide for hybridoma cell preparation for making monoclonal antibody with a reasonable expectation of success.

Claims 1 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al. (U.S. Patent 5,736,524, issued 04/07/1998) in view of Letesson et al. (Clin Diag Lab Immunol 4:556-564, 1997) and Ausubel (Short Protocols in Molecular Biology, 3rd Edition, Wiley & Sons Inc. 1995, see pages 16.3-5 and 16.58-62) and further in view of Harlow et al. (Antibodies, cold Spring Harbor Laboratory, 1988, page 561-552) and Neckelmann (FASEB J Vol. 12, pp. A1488, 1998).

Claim 1 is directed to a process for producing antibodies by (a) expressing a polypeptide which possesses at least one sequence encoding a detection signal, and binding the expressed polypeptide to a solid phase with the aid of the detection signal, (b) independently of step (a), introducing an expression vector comprising a nucleic acid encoding a polypeptide into an animal, wherein the animal produces antibodies against the expressed polypeptide, and (c) the antibodies produced in step (b) will be detected by binding the polypeptide bound to a solid phase of step (a); claim 13 is directed to the polypeptide bound to a solid phase in claim 1 is by means of the detection signal being bound to an antibody or an antibody fragment which is directed against it.

The process of producing antibody is rendered obvious in view of Content et al. ('524), Letesson et al. and Ausubel for the reasons previously discussed.

Letesson et al does not teach to bind an expressed polypeptide to a solid phase through an antibody which is bound to the detection signal.

However, Harlow et al. teach coupling antibodies to protein A beads (Harlow, page 521) or activated beads (Harlow, page 526) for binding antigen (Harlow, page 541), and Neckellman teach detection of His_6-tagged proteins by anti-His antibodies. Therefore, it would be prima facie obvious for a skilled artisan to couple anti-His antibodies to protein A beads or activated beads for binding of His_6-tagged polypeptide expressed with a reasonable expectation of success.

Claims 1 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al. (U.S. Patent 5,736,524, issued 04/07/1998) in view of Letesson et al. (Clin Diag Lab Immunol 4:556-564, 1997) and Ausubel (Short Protocols in Molecular Biology, 3rd Edition, Wiley & Sons Inc. 1995, see pages 16.3-5 and 16.58-62) and further in view of Harlow et al. (Antibodies, cold Spring Harbor Laboratory, 1988, page 561-552) and Neckelmann (FASEB J Vol. 12, pp. A1488, 1998).

Claim 1 is directed to a process for producing antibodies by (a) expressing a polypeptide which possesses at least one sequence encoding a detection signal, and binding the expressed polypeptide to a solid phase with the aid of the detection signal, (b) independently of step (a), introducing an expression vector comprising a nucleic acid encoding a polypeptide into an animal, wherein the animal produces antibodies against the expressed polypeptide, and (c) the antibodies produced in

step (b) will be detected by binding the polypeptide bound to a solid phase of step (a); claim 16 is directed the antibody which is reacted with the expressed polypeptide of claim 1 is released by elution.

The process of producing antibody is rendered obvious in view of Content et al. ('524), Letesson et al., Ausubel, Harlow et al. and Neckelmann for the reasons previously discussed. Harlow et al. further teach three types of elution of antigen by breaking the antigen-antibody interaction (Harlow, page 547-552). Although, Harlow et al. teach the elusion of antigen, the same principle applies to elution of antibody, which is to break the antigen-antibody interaction. Therefore, the skilled artisan would be able to elute antibody with a reasonable expectation of success.

Claims 1, 2, 5-7, 9-11, 13-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al. (U.S. Patent 5,736,524, issued 04/07/1998) in view of Whitehorn et al.(Bio/Technology, 13:1215-9, 1995).

Claims 1 and 7 are directed to a process for producing antibodies by (a) expressing a polypeptide which possesses at least one sequence encoding a detection signal, and binding the expressed polypeptide to a solid phase with the aid of the detection signal, (b) independently of step (a), introducing an expression vector comprising a nucleic acid encoding a polypeptide into an animal, wherein the animal produces antibodies against the expressed polypeptide, and (c) the antibodies produced in step (b) will be detected by binding the polypeptide bound to

a solid phase of step (a);, claim 2 is directed to the detection signal of claim 1 is at the C-terminus of the nucleic acid; claim 5 and 6 are directed to the expression vector of claim 1 comprises a strong promoter (claim 5) such as cytomegalovirus promoter (claim 6); claims 9 is directed the animal of claim 1 is a mouse; claims10-11 are directed to the process of claim 1 further comprises administering a genetic adjuvant (claim 10) such as cytokine (claim 11); claim 13 is directed to the polypeptide bound to a solid phase in claim 1 is by means of the detection signal being bound to an antibody or an antibody fragment which is directed against it; claim 14 is directed the solid phase of claim 1 is microtiter plate or magnetic beads; claim 15 is directed to the detection of the antibody produced by the animal of claim 1 using an antibody against the antibody after it binds to the polypeptide bound to a solid phase; and claim 17 is directed to the detection is a sequence which is responsible for membrane anchoring using a GPI residue.

Content et al. ('524) teach the production of antigen 85A-specific antibodies in DNA-vaccinated mice ('524, col. 5, line 33-34 and Fig. 9) by injecting a eukaryotic expression vector containing protein-coding DNA sequences ('524, col. 4, line 66 to col. 5, line 1, and col. 7, line 20-24) using different transcriptional promoter such as cytomegalovirus promoter ('524, col. 6, line 50-51, pertaining to instant claims 5-6) and terminators ('524, col. 6, line 25-28) into the animal. Moreover, Content et al. teach that the injected DNA can be naked ('524, col. 9, line 28), or can be injected with an adjuvant ('524, col. 9, 36-37) such as cytokines GM-CSF ('524, col. 9, line 22-

27, pertaining to instant claims 10-11). Content et al. further teach to provide a heterologous leader peptide sequence for secreted and/or membrane proteins ('524, col. 12, line 11-12). However, Content et al. dose not teach using GPI residue as detection signal for antibody detection.

Whitehorn et al. teach a general method for expression, purification, immobilization, detection and readiolabeling of extracellular domains (ECD) (Whitehorn, Abstract) by fusing the hydrophobic, C-terminal signal sequence derived from naturally phosphatidylinositol glycan (PI-G, it is GPI)-linked proteins to the C-terminus of the protein of interest. Proteins expressed in this way in mammalian cells (Whitehorn, page 1215, left col. third parag.) can be released from the cell surface by cleavage with PI-specific phospholipase C (PI-PLC) (Whitehorn, page 1217, left col. line 2-9). Whitehorn et al. further teach a monoclonal antibody (Ab179) that binds with high affinity to a portion of the C-terminal signal peptide fused to the expressed protein. This antibody binds the peptide epitope remains fused to the ECD after PI-PLC cleavage and can be targeted with labeled secondary reagents (Whitehorn, page 1217, left col. first full parag., pertaining to instant claim 15). Further more, Whitehorn et al. teach radioligand binding (Whitehorn, page 1217, left col. third full parag. and page 1218, right col. last parag.) to Ab179 immobilized receptor ECDs by coating microtiter plates with Ab179 (pertaining to instant claims 13-14) and incubated overnight with receptor-containing harvests, and bound radioactivity was eluted and counted (Whitehorn, page 1217, Fig. 4).

Whitehorn et al. cures the deficiency of Content et al. in that it teaches a method of fusing GPI as C-terminal signal sequence for expressed polypeptide to be linked to a solid phase for a further antibody binding detection.

One of skill in the art of antibody production will be motivated to combine the teachings of Content et al. ('524) with the teaching of Whitehorn et al. to fuse GPI residues derived from naturally PI-G-linked proteins to the C-terminus of the polypeptide of interest as tag sequence and express the fusion protein in mammalian cells so that cleavage of the tag sequence can result in secretion of the polypeptide of interest, and the secreted polypeptide can be used to bind to a solid phase by antibodies which recognize the tag sequence such as Ab179 (step a) for further detection of antibodies (step b) against the polypeptide of interest produced by an animal immunized by introducing a nucleic acid encoding the polypeptide. The level of skill in the art is very high, such that one of skill in the art would be able to combine the teaching of Content et al. ('524) and Whitehorn et al. with a reasonable expectation of success. Therefore, at the time the invention was made it would have been prima facie obvious to combine the teaching of Content et al. by detecting the antibody production using the method taught by Whitehorn et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liping Chen, whose telephone number is (703) 305-4842. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time). Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Pauline Farrier, Patent Analyst, at (703) 305-3550. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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